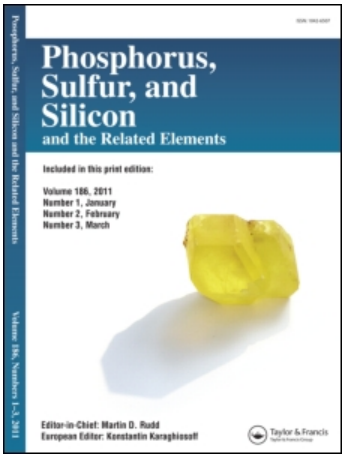

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EQUILIBRIA AND REACTION RATES OF PHOSPHORUS SUBSTITUTION REACTIONS IN 2-R-1,3,2-DISUBSTITUTED PHOSPHORINANES

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Equilibrium constants and reaction times were observed for six equilibria involving methanol, ethanol, dimethylamine, diethylamine and pyrrolidine with 2-R-1,3,2-dioxaphosphorinanes wherein R = MeO (**1**), EtO (**2**), Me_2N (**3**), Et_2N (**4**) and $(CH_2)_4N$ (**5**), or 2-R-1,3-dimethyl-1,3,2-diazaphosphorinanes wherein R equalled the same five groups (**6–10**, respectively). Reaction times of amine substitutions were shorter for diaza compounds and for those reactions which contained pyrrolidine. Equilibrium constants were dependent not only upon the nucleophilicities of the exchanging groups, but also upon the steric interactions of the 2-substituents with the groups in the 1 and 3 positions. Thus, the values of *K*'s for the equilibria **5** + $Me_2NH \rightarrow$ **3** + $(CH_2)_4NH$, and **10** + $Me_2NH \rightarrow$ **8** + $(CH_2)_4NH$ were experimentally identical, whereas K for **9** + $Me_2NH \rightarrow$ **8** + Et_2NH was *ca.* eight times that for **4** + $Me_2NH \rightarrow$ **3** + Et_2NH. The reactions were acid catalyzed, and, for amine substitutions with **8–10**, exchange could be rapid on the NMR time scale. Equilibrium positions of amine-containing reactions were $[H^+]$ dependent, where coordination of the less basic amine to phosphorus became increasingly favored by the addition of acid. These observations raise questions about a recent mechanistic proposal for catalyzed substitution reactions. Similar substitution reactions, such as Me_2NH with the isomeric 4-methyl analogues of **3**, provide a procedure for the determination of *cis-trans* isomer equilibrium distributions.

INTRODUCTION

There has been considerable interest in nucleophilic substitution reactions at phosphorus for the past several years.[1] The mechanism of exchange is now generally accepted to be S_N2 with rates being dependent upon the nucleophilicities of the exchanging groups.[1c] For example, when a phosphine containing the P—NR_2 link is combined with HNR'_2, a reaction which is first order in each reactant is observed; the reaction proceeds significantly only when the nucelophilicity of HNR'_2 (usually correlated with the free amine p*K* value) exceeds HNR_2; and the reaction rate increases with increasing amine basicities.[1c]

Substitution reactions are also known to be acid catalyzed[2] but no mechanism is generally accepted.[1a] Thus, in addition to the possibility of simple protonation of the phosphorus or coordinated amine, a third mechanism has been proposed recently.[1a] As depicted below for the exchange of dimethylamine by aniline, it has been suggested that the acid

$$R_2P{-}NMe_2 + HB \rightarrow R_2P{-}B + Me_2NH \xrightarrow{PhNH_2} R_2P{-}NHPh + Me_2NH_2{}^+B^-$$

HB first reacts with the dimethylamine-containing phosphine which in turn reacts with aniline. This was proposed because of the contention that a coordinated Me_2N— group could not be displaced by the much weaker nucleophile aniline (pK_b values of 3.3 and 9.4, respectively) whereas a coordinated B— group could.[1a]

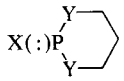
This paper reports the results of rate and equilibria studies of amino and alkoxy group substitution reactions in 1,3,2-dioxa- and diazaphosphorinanes. The data indicate that exchanges can be extremely facile, suggest that steric as well as electronic factors can be important in exchange processes, raise questions about the recently proposed mechanism of acid catalysis (*vide supra*), and point to a convenient procedure for obtaining equilibrium distributions of *cis* and *trans* isomeric phosphorinanes.

RESULTS AND DISCUSSION

The equilibrium and rate data for compounds **1–5** and **8–10** (Table 1) are presented in Table II.

Data for compounds **6** and **7** are not included since their substitution reactions resulted in ring cleavage. This phenomenon has also been previously

TABLE I
2-R-1,3,2-disubstituted phosphorinanes



Compound	X	Y	Compound	X	Y
1	MeO	O	**6**	MeO	NMe
2	EtO	O	**7**	EtO	NMe
3	Me_2N	O	**8**	Me_2N	NMe
4	Et_2N	O	**9**	Et_2N	NMe
5	$(CH_2)_4N$	O	**10**	$(CH_2)_4N$	NMe

reported for the reactions of alcohols with other 1,3,2-diazaphosphorus heterocycles.[1b] The equilibrium data were obtained for the reactions as written and their reverse. Times listed are approximately those required to establish equilibrium.

The reaction rates can be seen to be highly dependent on the electronic properties of both exchanging and static phosphorus substitutents and upon the presence of acid. Those reactions involving pyrrolidine proceeded more rapidly than those containing the other two amines only (e.g., reactions C *vs.* B). This behavior has been reported by other workers as well and is presumably due to the greater basicity of pyrrolidine (pK_b of pyrrolidine 2.7, diethylamine 2.9, and dimethylamine 3.3).[1c] The rates were also dependent upon the non-exchanging phosphorus substituents, wherein those for the diaza compounds were consistently more rapid than those of the dioxa compounds (e.g., reactions E *vs.* C, and D *vs.* B). The reasons for this are not understood, however. Acid catalysis has been previously reported,[2] but the potential effects of acid have not been full recognized. The catalysis is $[H^+]$ dependent, and, for the diaza compounds, exchange can be rapid on the NMR time scale. For example, upon incremental addition of *p*-toluenesulfonic acid to a solution of **8** and dimethylamine in benzene, the methyl doublet of the coordinated Me_2N- group and the methyl singlet of free Me_2NH broadened and eventually collapsed into a single peak.

The equilibrium data contained in Table II indicate that in the absence of acid neither alkoxy group is particularly favored (reaction A), but the amino groups display considerable preferences which can be dependent both upon the pair of amines employed (e.g., reaction B *vs.* C) and upon the ring substituents (reaction B *vs.* D). There are two important considerations for the interpretation of these results, the relative stabilities of the exocyclic P—X bonds, and steric interactions between X and the other groups attached to phosphorus. In the absence of the latter, the P—X bond strength is expected to be reflected by the pK_b values of the free amines.[1] Thus, a coordinated Et_2N- group should be favored over a coordinated Me_2N- group. In the presence of substantial steric hindrance, however, the less demanding Me_2N- group would be preferred. As reported previously from observations of models of dioxa and diaza compounds, steric interactions are important in the former[3] and critical in the latter.[4] The data reported here reflect this wherein the coordinated Me_2N- group is favored in both systems, but to a much greater extent in the sterically more demanding diaza one ($K = 25$ *vs.* 3.4). In contrast to Et_2N-, a coordinated $(CH_2)_4N-$ group has steric requirements very similar to Me_2N- in addition to a greater free amine basicity. It is therefore expected and seen, that coordinated $(CH_2)_4N-$ is favored over Me_2N- to a similar extent in the two heterocyclic systems ($K = 0{\cdot}45$ for both). For the alcohols, the equilibrium value of coordinated EtO— *vs.* MeO— is near one in the dioxa compounds. This is probably due in part to the reduced steric requirements of the alcohols compared to their amine analogues.

TABLE II
Equilibrium and rate data

Reaction	Starting materials → products	Without added acid		With added acid[a]	
		K	Time	K^b	Time
A	**2** + MeOH → **1** + EtOH	1.4 ± 0.5	20 days	1.5 ± 0.5	<15 min
B	**4** + Me_2NH → **3** + Et_2NH	3.4 ± 0.5	20 days	4.8 ± 0.5	2 days
C	**5** + Me_2NH → **3** + $(CH_2)_4NH$	0.45 ± 0.05	3 days	>0.45	<2 hrs
D	**9** + Me_2NH → **8** + Et_2NH	25 ± 5	<15 min	—	Rapid[c]
E	**10** + Me_2NH → **8** + $(CH_2)_4NH$	0.45 ± 0.05	<15 min	—	Rapid[c]

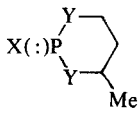
[a] *p*-toluenesulfonic acid, *ca.* 1%.
[b] Not actually equilibrium constants, see text.
[c] Rapid on the nmr time scale.

The equilibrium data obtained from the acid-containing samples as listed in Table II are not true equilibrium constants. The concentrations of free amines and alcohols were not distinguished from protonated species potentially present in the solutions (e.g., $Me_2NH_2^+$ in reaction B). This allows for direct identification of the effect of acid upon distributions of coordinated and uncoordinated groups. The equilibrium data obtained in this manner, however, are $[H^+]$ dependent. The value listed for B is therefore not unique, but was chosen as being representative of the effect of small quantities of acid. Equilibrium distributions could not be determined quantitatively for reactions C and E since the proton chemical shifts of the coordinated and protonated pyrrolidine were nearly identical. The effects of acid were observed qualitatively, however, from the Me–N peaks. Data from the diaza compounds **6–10** could not be obtained because even small quantities of acid caused rapid exchange and partial collapse of nmr spectral peaks.

The alcohol equilibria were affected little by added acid, but the amine equilibria were shifted toward formation of coordinated Me_2N–. These observations can be rationalized by consideration of the protonated species formed in the solutions. For reactions B and C, the likely species are protonated amines whose stabilities are indicated by the pK_b values. In the presence of acid, $Et_2NH_2^+$ and $(CH_2)_4NH_2^+$ are therefore formed in preference to $Me_2NH_2^+$, resulting in the equilibria being shifted toward additional coordinated Me_2N–. As more acid was added, the equilibria were shifted more toward coordinated Me_2N– until eventually the solubility of at least one amine salt was exceeded, precipitation commenced, and the equilibrium positions began to shift back toward the formation of coordinated Et_2N– in reaction B, and coordinated $(CH_2)_4N$– in reaction C. Additional acid continued this trend. This apparently resulted from removal of the less soluble dimethylamine salt by precipitation with concomitant coordination of the other amine. The protonation of MeOH and/or EtOH, on the other hand, must either be unimportant or occur to nearly identical extents.

This study does not provide the necessary data to identify the mechanism of acid catalysis, but it does raise questions about the recent proposal described in the Introduction which has been suggested because of the contention that the coordinated Me_2N– group could not be displaced by aniline. In this study, however, it has been seen from reactions B through E that equilibria are attainable by starting with either coordinated amine of a given pair and that the equilibria were readily shifted by the addition of acid. These observations suggest that even in the case of Me_2NH and aniline, where the pK_b values differ greatly, an equilibrium exists but is positioned so as to make coordinated PhHN– unobservable. In the presence of acid the equilibrium would then be shifted dramatically toward the formation of the more stable $Me_2NH_2^+$ salt and coordinated PhHN–. An intermediate P–B type of compound is unnecessary to explain the results.

TABLE III
Isomeric 2-substituted-1,3,2-phosphorinanes



Compound	X	Y	Compound	X	Y
11a (*trans*)	Me_2N	O	**12a** (*trans*)	Me_2N	NMe
11b (*cis*)	Me_2N	O	**12b** (*cis*)	Me_2N	NMe
			13a (*trans*)	MeO	NMe
			13b (*cis*)	MeO	NMe

The types of exchange reactions reported here also appear to be convenient for the determination of equilibrium distributions in isomeric compounds such as **11a,b–13a,b**. Freshly prepared **11a,b** can be obtained only as mixtures of isomers which may vary in **a**:**b** isomer ratio from about 30:70 to 15:85 (see Experimental Section). A distribution of the former magnitude requires several days before the equilibrium ratio of 15:85 is obtained.[5] Upon the addition of Me_2NH and a small quantity of acid, a distribution of 17:83, which is probably within experimental error of 15:85, was observed in about 2 days. This reaction time is consistent with the data for the similar reaction B. In contrast to **11a,b** it has been proposed[4] that even freshly prepared samples of **12a,b** and **13a,b** exist as their equilibrium distributions. This is supported here by the fact that even after several days in the presence of dimethylamine, no change in isomer distribution of **12a** to **b** was detectable. (The addition of acid resulted in rapid exchange on the nmr time scale.) Based on the data in Table II for reaction D, which involves similar compounds, any change should have occurred in less than 15 min. The reaction of **13a** and **b** with methanol was accompanied by ring cleavage. During that process, however, no change in isomer distribution was observed, again suggesting that the

original distribution was that of equilibrium. That **12a,b** has been obtained only as the equilibrium distribution but **11a,b** can be obtained enriched in one isomer is likely due to the more rapid exchange of the exocyclic groups in the diaza compounds. Both isomeric pairs were obtained from the reaction of their respective cyclic P—Cl compounds with excess dimethylamine. The presence of the excess amine and amine hydrochloride, the other reaction product, apparently allows for the rapid equilibration of **12a** and **b** but not necessary for that of **11a** and **b**. Alternative preparative routes may allow for enrichment of one of the isomers of **12**. Thus, the possibility of rapid exchange in tricoordinate phosphorus starting materials appears to be an important consideration in stereospecific reaction sequences.

EXPERIMENTAL

Syntheses: The preparation of these and similar dioxa-[3,6] and 1,3,2-diazaphosphorianes[4,7] have been previously described from their respective cyclic P—Cl compounds and alcohol or amine. Previously unreported, however, is that the distributions of freshly prepared **11a** and **b** were found to vary from about 30:70 to 15:85 in a manner that was not reproducible.

Equilibrium data: The values of K were determined from both forward and reverse reactions by integration of proton nmr spectra (Varian T-60 instrument) of room temperature benzene solutions *ca.* 10% in all reactants except acid. For the acid catalyzed reactions solutions were rendered *ca.* 1% in *p*-toluenesulfonic acid.

Rate data: Times reported are approximately those required for the establishment of equilibrium.

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